EFFERVESCENT PHARMACEUTICALS

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INTRODUCTION

Effervescent tablets are uncoated tablets that generally contain acid substances and carbonates or bicarbonates, and that react rapidly in the presence of water by releasing carbon dioxide. They are usually dissolved or dispersed in water before administration (1).

Effervescent mixtures have been known for over 250 years. During the 1930s, the success of Alka Seltzer created a vogue for effervescent products, including tablets (2). Effervescent tablets have been reviewed (3–5).

Effervescent reactions have also been employed in other dosage forms, such as suppositories (laxative effect), vaginal suppositories (mainly contraceptive effect), and drug delivery systems (e.g., floating systems and tablets rapidly dissolving in the saliva).

Effervescent products should be stored in tightly closed containers. Desiccants are usually added to the containers.

PHARMACOPEIAL MONOGRAPHS

Soluble, effervescent tablets are prepared by compression. In addition to active ingredients, they contain mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate ($NaHCO_3$) that release carbon dioxide when dissolved in water (6). The *United States Pharmacopeia* (USP) 24 includes the following seven monographs: Acetaminophen for Effervescent Oral Solution; Aspirin Effervescent Tablets for Oral Solution; Potassium Bicarbonate Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid for Oral Solution; and Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution (7).

Effervescent tablets as well as effervescent granules and powders are mentioned in the *European Pharmacopoeia* (Ph. Eur.), although it does not contain any monographs regarding specific drugs (1, 8).

THE EFFERVESCENT REACTION

Acid–base reactions between alkali metal bicarbonate and citric or tartaric acid have been used for many years to produce pharmaceutical preparations that effervesce as soon as water is added. In such systems, it is practically impossible to achieve much more than an atmospheric saturation of the solution with respect to the released carbon dioxide. If the acid dissolves first, then the bulk of the reaction takes place in the saturated solution in close proximity to the undissolved bicarbonate particles. If the bicarbonate dissolves faster, the reaction essentially takes place near the surface of the undissolved acid. Such suspension systems do not favor supersaturation with respect to carbon dioxide because the particulate solids act as nuclei for bubble formations (9).

RAW MATERIALS

General Characteristics

With regard to compressibility and compactibility, the considerations pertaining to raw materials in effervescent products are similar to the ones that prevail in evaluating raw materials intended for conventional tablets. However, poor compactibility cannot usually be compensated for by the use of binders, as this will prevent a rapid dissolution of the effervescent tablet. Addition of a binder is generally not as critical for the dissolution of effervescent granules or powders.

The general tablet compaction process normally is described by a number of sequential phases: rearrangement, deformation (elastic, plastic) of initial particles, fragmentation, and deformation of fragments. Particle surfaces are

brought into close proximity and interparticulate attraction or bonds will be formed (10). Similar conditions will prevail with the effervescent tablets.

A very important property for effervescent products is the adsorption/desorption isotherm of the raw material and, consequently, its moisture content. To avoid a premature effervescent reaction in the tablets, substances with low moisture contents will have to be used. The aqueous solubility is another important property of the substances used in effervescent products. It is also important to use raw materials that are easily wetted. Of course, the taste of the employed substances is important.

Acid Materials

The acidity for the effervescent reaction can be obtained from three main sources: acids, acid anhydrides, and acid salts. Traditional sources of acid materials are the organic acids, citric and tartaric acid; however, some acid salts also are used.

Acids

Citric acid: Citric acid is obtained as a monohydrate or an anhydrate. A variety of particle-size grades are available—colorless, translucent crystals, or white, granular-to-crystalline powder. Citric acid is odorless and has a strong acidic taste. It is soluble in less than 1 part of water and 1 in 1.5 parts of ethanol (11).

Citric acid monohydrate melts at 100°C. It loses water at 75°C, becomes anhydrous at 135°C, and fuses at 153°C. At relative humidities (RH) lower than approximately 65%, it effloresces at 25°C; the anhydrous acid is formed at humidities below approximately 40%. At RH between approximately 65 and 75%, it sorbs insignificant amounts of moisture, but above this, substantial amounts are absorbed (Fig. 1) (11).

Figure 1 also includes the sorption curve of the anhydrate. The anhydrous form melts at 135°C during decomposition (12). At RH approaching 75%, the monohydrate is formed (11).

Information from Heckel plots indicates that anhydrous citric acid is predominantly fragmented during compression (13). The elastic deformation and consequently the elastic recovery during decompression are low (14).

Tartaric acid: Tartaric acid is soluble 1 in 0.75 parts of water, and 1 in 2.5 parts of alcohol (15). It sorbs insignificant amounts of moisture at RH up to approximately 65%, but at RH above approximately 75%, substantial amounts are absorbed (Fig. 1).

Studies indicate that tartaric acid behaves in a manner similar to that of anhydrous citric acid. During compression, the acid fragments predominantly, and the elastic deformation and consequently the elastic recovery were low (14).

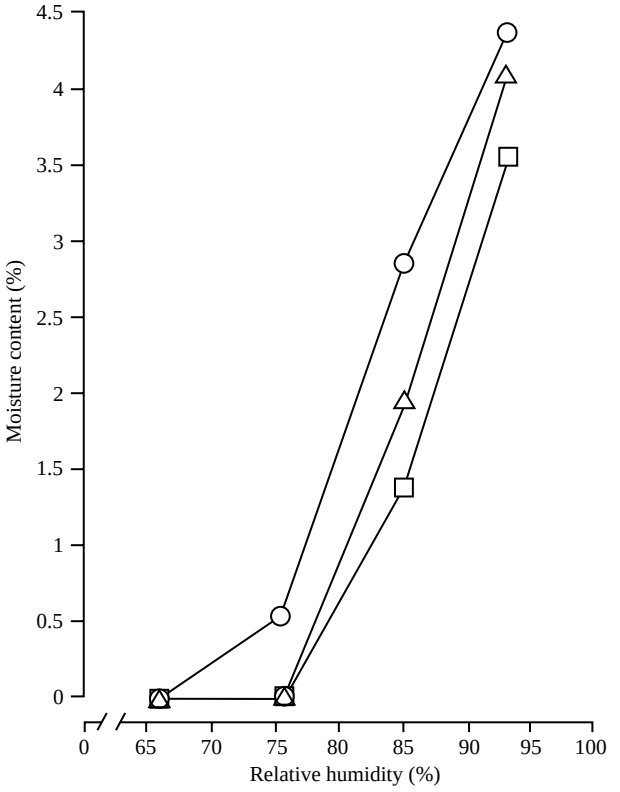

Fig. 1 Sorptionisotherms of some hygroscopic acids. *Key*: *x* axis = relative humidity, %; *y* axis = moisture content, %; ○ = citric acid monohydrate; Δ = anhydrous citric acid; □ = tartaric acid. (Adapted from Ref. 16.)

A comparison of the formation of carbon dioxide from effervescent tablets based on anhydrous citric acid, ascorbic acid or tartaric acid, and $NaHCO_3$ in stoichiometric proportions indicated that ascorbic acid and anhydrous citric acid behaved similarly. However, tartaric acid formed the most carbon dioxide, but the disintegration time was longer (16).

Ascorbic acid: Ascorbic acid occurs as white to light yellow crystalline powder or colorless crystals with a sharp, acidic taste and no odor. It is not hygroscopic. Upon exposure to light, it gradually darkens. Ascorbic acid is soluble 1 in 3.5 parts of water and 1 in 50 parts of ethanol (17).

Ascorbic acid particles show an intermediate fragmentation during compaction. The relatively low tablet strength indicates that the attraction forces are relatively weak and not very resistant to stress relaxation and elastic recovery (18).

Ascorbic acid can be used as the acid source. The speed of release of carbon dioxide from a mixture of ascorbic acid and

$NaHCO_3$ is comparable with that produced by citric or tartaric acid–$NaHCO_3$ combinations. Since ascorbic acid is less hygroscopic than citric and tartaric acid, using ascorbic acid as the only acid source makes it possible to produce effervescent tablets in a nonairconditional area (19).

Fumaric acid: Fumaric acid is a white, odorless or nearly odorless crystalline powder. It is soluble 1 in 222 parts of water and 1 in 28 parts of ethanol (20). The sorption isotherm indicates that fumaric acid is not a hygroscopic substance (16).

Acetylsalicylic acid (aspirin): Although acetylsalicylic acid is a drug frequently used in effervescent form, it cannot be used as the acid source because of its low water solubility. Additional acid is necessary to decrease the reaction time.

Other acids: Malic acid is hygroscopic and readily soluble in water. It has been suggested for effervescent products (3).

Other acids have been mentioned in connection with effervescent products (3, 5).

Acid anhydrides: The use of acid anhydrides as the acid precursor has been investigated. However, their use in commercial products is limited.

Acid salts: Amino acid hydrochlorides readily release acid when in solution. However, these materials have the disadvantage of being expensive and rather hygroscopic (4). Other suggested acid sources include: sodium dihydrogen citrate (21), a nonhygroscopic substance (16); disodium hydrogen citrate, which is nonhygroscopic below approximately 93% RH/20°C (16); and sodium acid phosphate, which is very soluble in water.

Sources of Carbon Dioxide

Both carbonates and bicarbonates are used as carbonate sources, but the latter is most often used.

Sodium bicarbonate ($NaHCO_3$)

$NaHCO_3$ is an odorless, white crystalline powder with a saline, slightly alkaline taste. A variety of particle-size grades of powders and granules are available. The carbon dioxide yield is approximately 52% by weight. At RH below approximately 80% (at room temperature), the moisture content is less than 1%. Above 85% RH, it rapidly absorbs an excessive amount of water and may start to decompose. Its solubility in water is 1 part in 11 parts at 20°C, and it is practically insoluble in 95% ethanol at 20°C. When heated to 250–300°C, $NaHCO_3$ decomposes and is converted into anhydrous sodium carbonate. However, this process is both time- and temperature-dependent, commencing at about 50°C. The reaction proceeds via surface-controlled kinetics, and when $NaHCO_3$ crystals are heated for a short period of time, very fine needle-shaped crystals of anhydrous sodium carbonate appear on the surface (22).

In humid air, there is a slow decarboxylation of $NaHCO_3$, where as sodium sesquicarbonate $Na_2CO_3 \cdot NaHCO_3 \cdot 2H_2O$ is formed (23).

$NaHCO_3$ mainly consolidates by plastic deformation and not by fragmentation (18). It is a nonelastic substance (13).

In order to overcome the poor flowability and low compressibility of $NaHCO_3$, a spray-drying technique was used. Additives such as polyvinylpyrrolidone and silicon oil were found to be essential to obtain direct compressible spray-dried $NaHCO_3$. The product showed good compression characteristics without being transformed into sodium carbonate (24).

Sodium carbonate: Sodium carbonate is commercially available as an anhydrous form and as a monohydrate or a decahydrate. All forms are very soluble in water. The anhydrate is hygroscopic (25).

Potassium bicarbonate: Potassium bicarbonate ($KHCO_3$) is very soluble in water. When heated to approximately 200°C, it is decomposed, and potassium carbonate, water, and carbon dioxide are formed (26). Consequently, $KHCO_3$, is less sensitive to heat in connection with drying than is $NaHCO_3$. Above approximately 80% RH at 20°C, substantial amounts of water are adsorbed by $KHCO_3$.

Potassium carbonate: The moisture scavenging effect of potassium carbonate in effervescent tablets has been investigated (27).

Calcium carbonate: Precipitated calcium carbonate occurs as fine, white, odorless, and tasteless powder or crystals. It is practically insoluble in water and ethanol (95%). Precipitated calcium carbonate is nonhygroscopic (28). Calcium carbonate is a high-density, not very compressible material (29). It is known to consolidate by fragmentation (30).

Other sources: Amino acid–alkali metal carbonate derivatives, such as sodium glycine carbonate, have been suggested as sources of carbon dioxide.

Sodium glycine carbonate is a nonhygroscopic, heat-resistant, stable substance (31). However, the carbon dioxide yield—approximately 18% by weight—is only about one-third of $NaHCO_3$.

PRODUCTS

Dosage Forms

Effervescent tablets (1, 6), granules, and powders (8) are mentioned in the pharmacopoeias and exist as products

on the market. The effervescent tablet provides several advantages over conventional oral solid dosage forms. It is administered as a reasonably palatable, sparkling solution. Consequently, it can be given to patients who have difficulties swallowing capsules or tablets. Since the drug is administered as a solution, problems associated with dissolution, that is, absorption rate and extent of bioavailability, are avoided. Drugs that are unstable when stored in aqueous solutions are more often stable in the effervescent tablet.

Effervescent dosage forms have several drawbacks when compared with aqueous solutions and plain tablets. For example, they are relatively expensive to produce due to the use of large amounts of more or less expensive excipients and the necessary special production facilities, as well as high $Na+$ and/or $K+$ concentrations. In addition, when compared with plain tablets, effervescent tablets are bulky, even though small packages that are easy to carry in a pocket or handbag are available. Finally, it is sometimes difficult to make unpleasant tasting drugs sufficiently palatable in an effervescent form.

When an effervescent product is dropped into a glass of water, the reaction between the acid and the $NaHCO_3$ is quite rapid, usually completed within 1 minute or less (32). The effervescent reaction is also used in other pharmaceutical dosage forms than the traditional effervescent products. Effervescent laxative suppositories that release carbon dioxide have been thoroughly studied (33). One product has been on the Swedish market for many years. Effervescent vaginal suppositories are described (34). Pulsatile and gastric floating drug delivery systems for oral administration based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating also have been investigated (35).

Drugs (Product Categories)

Many drugs and drug compositions have been used for effervescent products. Some of these are listed below.

Acetylsalicylic acid (aspirin) is a common drug in many different effervescent products (36, 37).

Paracetamol (acetaminophen) is another analgesic used in effervescent preparations (38).

Effervescent compositions of ibuprofen, another analgesic, are marketed.

Among effervescent antacid preparations, Alka-Seltzer, an effervescent antacid analgesic product, has been available since the 1930s. Pure effervescent antacid products are marketed in many countries.

Effervescent tablets of ascorbic acid, 0.5–1 g, are well known. Other vitamins as well as calcium and some minerals have also been included.

Acetylcysteine, a mycolytic agent that also is used as an antidote for paracetamol overdose, is available as an effervescent tablet.

Effervescent products of water-insoluble drugs have been manufactured. A successful example is the effervescent activated charcoal preparation suggested in the management of theophylline poisoning (39).

Electrolyte Balance Considerations

Effervescent tablets normally have a high sodium content. In most of the effervescent analgesic products in Sweden, the sodium content is approximately 15 mmol. This sodium content may be contraindicated in some patients (e.g., in patients with active sodium-retaining status such as congestive heart failure or renal insufficiency). Otherwise, there are no restrictions concerning the sodium content of effervescent tablets.

Biopharmaceutical Aspects

Drugs are most rapidly absorbed from the gastrointestinal (GI) tract when administered as aqueous solutions. Although dilution of the drug solution in the gastric fluids sometimes results in precipitation, the extremely fine nature of the precipitate permits rapid redissolution (40). The rapid absorption of the aqueous solution is the idea behind effervescent analgesic products, for example. Furthermore, consistent absorption is expected with the solution, as disintegration and dissolution in the GI tract are bypassed.

Effervescence may produce physiological changes within the body. Carbon dioxide bubbling directly onto the intestinal epithelium induced enhanced drug permeability due to an alteration of the paracellular pathway. This, in addition to fluid flow and membrane hydrophobicity concepts, may account for observed increases in drug flux (41).

Buffered effervescent aspirin tablets are generally believed to have a less irritant effect on the gastric mucosa and cause less GI blood loss than conventional tablets. This view has been questioned.

The bioavailability of acetylsalicylic acid from three different dosage forms—two types of effervescent tablets with different buffering properties and tablets of a conventional type—was studied in healthy volunteers. Complete absorption was found for all the preparations

studied. Both effervescent tablets were rapidly absorbed. The buffering properties did not influence the rate of absorption (36).

Effervescent aspirin, soluble aspirin, and soluble aspirin to which sufficient $NaHCO_3$ had been added to give it the same buffering capacity as the effervescent preparation, were compared in healthy volunteers. There were no significant differences in plasma salicylate levels at any time after taking these preparations (37).

The absorption of the effervescent formulation of paracetamol was compared with that of a plain tablet in normal volunteers. As to the rate of absorption, this was more rapid and consistent from the effervescent preparation than from the plain tablet. This may have important therapeutic implications where a rapid and predictable analgesic effect may be desired (38).

The bioavailability of an effervescent ibuprofen tablet was compared to a sugar-coated tablet. Ibuprofen was absorbed more rapidly from the effervescent tablet but both formulations were bioequivalent in respect to peak plasma concentrations and area under the plasma concentration curves (42).

PROCESSING

Environment

The manufacturing of effervescent tablets requires careful control of environmental factors. As early as the 1930s, it was clear that it was essential to maintain RH throughout the plant of no more than 20%. In addition, a uniform temperature of 21°C also was desirable (2).

A maximum of 25% RH at a controlled room temperature of 25°C or less is usually sufficient to avoid problems caused by atmospheric moisture (3).

Equipment

Conventional processing equipment (mixers, granulators, roller compactors, drying equipment, and mills) can be used to produce effervescent preparations if the influence of atmospheric moisture is considered. As a rule, tablet presses have to be adapted to handle effervescent products, except for tablets with a sufficient proportion of a self-lubricating substance, such as acetylsalicylic acid.

Wet Granulation Methods

The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (crystal water of citric acid, liquid water, or water vapor), ethanol (possibly diluted with water), isopropanol, or other solvents.

When granulating with solvents without any moisture, no effervescent reaction will occur provided the raw materials are dry and the process is performed in a low humidity atmosphere. However, citric acid will partly dissolve in ethanol or isopropanol, and function as a binder when the solvent is evaporated.

When granulating either with solvents containing water or pure water, the effervescent reaction will start. Care must be taken to maintain adequate control of the process. Vacuum processing is often beneficial due to the ability to control the effervescent reaction and the drying process.

In the fusion method of granulation, the effervescent mixture is heated to approximately 100°C (the melting point of the monohydrate) so that the water of crystallization from hydrous citric acid is released. This process is sporadic and difficult to control, especially in a static bed (3).

By means of high-shear mixers and the heat generated during mixing, it was possible to prepare granular effervescent products in batch sizes of 60–300 kg using the fusion method (43).

Citric acid is moistened and added to the $NaHCO_3$. Partial wet fusion occurs, and granules are formed by kneading in a suitable mixer. The granules are tableted while still damp, with the moist citric acid acting as a lubricant. The compressed tablets are transferred immediately and continuously to ovens where they are dried at 70–75°C. Drying also hardens them. As soon as they leave the dryer, the tablets are packed in aluminum foil lined with polyethylene (44).

X-ray diffractometry and infrared (IR) spectrophotometry were used to study the reaction between citric acid and $NaHCO_3$ when granulating the mixture with water in a high-shear mixer and vacuum drying the wet mass. The contact time before drying varied as did the water content. At low water levels, varying the contact times did not change the citric acid. However, with higher levels of water content, the presence of monocitrates, dicitrates, and tricitrates was verified. The loss of carbon dioxide during granulation occurred in the presence of, especially, dicitrates and tricitrates (45).

Effervescent granules were prepared in a fluid bed granulator/dryer (46).

The drug can be mixed with the effervescent granulate and other excipients or be a part of the granulation. When mixing low proportions of drug with granulate, the risk of segregation must be taken into account.

Dry Granulation

Granulation by slugging (slugs or large tablets that are compressed using heavy-duty tableting equipment) or roller compaction is suitable for materials that cannot be wet granulated. The slugs and the material from the roller compactor are reduced to the proper size. Lubrication is often necessary during slugging but not always with roller compaction. The acidic and basic components may be dry granulated separately or together.

Direct Compression

Some effervescent tablet products are successfully produced by direct compression (e.g., acetylsalicylic acid products). Direct compression normally requires careful selection of raw materials to achieve a free-flowing, nonsegregating, compressible mixture. Effervescent products present the same problems as conventional products in direct compression.

Tableting

The adaptation of a single-punch tablet press for compressing effervescent tablets via external lubrication has been described (5, 47). Only rotary presses are normally used in connection with the commercial production of effervescent tablets. Tablet machine manufacturers have applied various adaptations to their existing equipment to avoid problems due to internal lubrication and punch adhesion. Consequently, many effervescent tablets are produced on rotary presses with external lubrication. Liquid or solid lubricants can be used.

FORMULATION

Excipients (Including Sweeteners and Flavors)

Lubricants

A perfect lubricant (or auxiliary agent, in general) for effervescent products must be nontoxic, tasteless, and water-soluble. Very few traditional lubricants fulfill these requirements.

Intrinsic lubricants are added to the powder mixture and consequently included in the formulation. When added in solid form, the lubricant will have to be finely divided.

Metal stearates, such as magnesium or calcium stearate that serve as lubricants in conventional tablets, are seldom used as intrinsic lubricants in connection with effervescent tablets due to their insolubility in water. Use of stearates results in an undissolved, foamy, soapy-tasting layer on the surface of the cloudy solution. In addition, normal lubricant concentrations of metal stearates make the tablets hydrophobic, which entails a slow dissolution of the effervescent tablet in the water. However, very low concentrations of metal stearates can be used to improve the rate of solution of effervescent tablets as the tablet will remain immersed in the water during dissolution and not float to the surface the way a tablet without metal stearate would. A floating tablet presents a smaller surface area to the water than a tablet immersed in the liquid.

Sodium stearate and sodium oleate are water-soluble in low concentrations. They have the characteristic soapy taste, which virtually precludes their use in effervescent products.

A combination of 4% polyethylene glycol (PEG) 6000 and 0.1% sodium stearyl fumarate proved to be a good lubricant for ascorbic acid tablets made by direct compression on a small scale (48). Sodium chloride, sodium acetate, and D,L-leucine (water-soluble lubricants) also have been suggested for effervescent tablets (44).

Twenty lubricants for effervescent tablets were tested for lubrication efficiency in direct compression of a standard effervescent formulation. The lubricant concentration was high as compared to traditional tablet lubricants. By increasing the lubricant concentration and the compression force, most lubricants became more effective. The lubricant used in effervescent formulations should combine hydrophobic and hydrophilic properties in order to achieve both good lubrication and a short disintegration time. A medium polar lubricant was the best compromise. Fumaric acid was chosen and its concentration optimized (49). Other research that studied the lubrication of effervescent products indicated optimal concentrations of spray-dried L-leucine and PEG 6000 at levels of 2 and 3%, respectively (50).

Surfactants such as sodium lauryl sulfate and magnesium lauryl sulfate also act as lubricants.

Extrinsic lubrication is provided via mechanisms that apply a lubricating substance, normally paraffin oil, to the tableting tool surface during processing. One method makes use of an oiled felt washer attached to the lower punch below the tip. This washer wipes the die cavity with each tablet ejection. To avoid having tablets stick to the punch faces, materials such as polytetrafluorethylene or polyurethane have been applied to the faces. Another lubrication method sprays a thin layer of lubricant (either liquid or solid lubricant) onto the tool surfaces after one tablet is ejected and before the granulate of the next tablet enters the die cavity.

Products containing acetylsalicylic acid do not usually require additional lubrication.

Glidants

Glidants are usually not necessary. Free-flowing granulates, ingredients of appropriate physical form for direct compression, and the large tablet diameters make it possible to exclude the use of glidants.

Antiadherents

The adherence of the granulate or powder mixture to the punch surfaces, so-called picking, can be eliminated by using discs, such as polytetrafluorethylene or polyurethane, cemented to the punch surfaces.

Binders

Binders are commonly used when making conventional tablets. The binders are either added in dry form or dissolved in a suitable solvent and then added in connection with a wet-granulation process. Most binders are polymers and increase the plastic deformation of the formulation.

The use of binders will normally prevent a rapid dissolution of the effervescent tablet. Therefore, many effervescent tablets are formulated without any binder. However, effervescent granules may be formulated with binders since their large surface area, when compared with that of the conventional or the effervescent tablet, will result in rapid dissolution. An effervescent granulation composed of anhydrous citric acid and $NaHCO_3$ was made with dehydrated alcohol as the granulating liquid. A portion of the citric acid dissolved during the massing and functioned as a binder (51).

In order to compress ascorbic acid from a combination with $NaHCO_3$, granulation was required. Common water-soluble binders, such as polyvinylpyrrolidone (polyvidone) or polyvinylpyrrolidone–poly(vinyl acetate)-copolymer, led to a change of color on the part of the ascorbic acid granules. Hydrogenated maltodextrins containing high amounts of maltitol were chosen from a wide range of dextrins and maltodextrins as possible binders. Maltitol was a suitable binder for ascorbic acid effervescent tablets. Formation of crystal bridges of maltitol was the assumed binding mechanism (19). PEG 6000 functions both as a binder and as a lubricant.

Disintegrants or dissolution aids

Disintegrants, which are used in conventional tablets, are not normally used in effervescent tablets because one of the marketing demands is that a clear solution should be obtained within a few minutes after adding the tablet to a glass of cold water.

Diluents

Effervescent products generally do not require diluents. The effervescent materials themselves will have to be added in large quantities.

Sweeteners

Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products, although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Therefore, the use of such sweeteners will vary from one country to the next based on national standards.

Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted.

Flavors

The simple use of sweetening agents may not be sufficient to render palatable a product containing a drug with an unpleasant taste. Therefore, a flavoring agent can be included. Various dry flavors are available from suppliers. The flavors used must be water-soluble or water-dispersible.

Colors

Water-soluble colors may be added; however, some dyes change color according to pH variations, a consideration that must be noted before a dye is selected.

Surfactants

This type of excipient is sometimes used to increase the wetting and dissolution rate of drugs. Attention must be paid to the formation of foam.

Antifoaming agents

To reduce the formation of foam, and consequently the tendency of drugs to stick to the wall of the glass above the water level, an antifoaming agent, such as polydimethylsiloxane, can be used. However, antifoaming agents do not normally form constituents of effervescent products.

Formulations (Including Optimization)

Literature on formulations of effervescent products it relatively sparse. Table 1 presents some examples of effervescent products on the Nordic market.

A fractional factorial design was employed in the preparation of effervescent aspirin tablets. The optimum conditions for preparing the tablets were determined following the path of steepest ascent (53).

Table 1 Some compositions of effervescent tablets on the Nordic market: Components and weight per tablet

	Product A		Product B		Product C	
	Component	**mg**	**Component**	**mg**	**Component**	**mg**
Drugs	Ascorbic acid	1000	Acetylsalicylic acid	500	Paracetamol	500
			Caffeine	50		
Excipients	Citric acid, anhydrous	700	Citric acid, anhydrous	500	Citric acid, anhydrous	1200
	Sodium bicarbonate	490	Sodium bicarbonate	1250	Sodium bicarbonate	1550
	Polyethylene glycol 6000	45	Docusate sodium	0.85	Polyvidone	25
			Sodium benzoate	0.15	Sodium cyclamate	45
	Sorbitol	25			Saccharin sodium	5
	Saccharin sodium	12			Lemon flavor	25
	Riboflavin sodium phosphate (for color)	1			Magnesium stearate	1.4
	Orange flavor	2				

(Adapted from Ref. 52.)

An experiment investigating the effects of tablet manufacturing conditions, tablet formulations, tablet compression pressures, storage conditions, and storage times was performed on five different formulations (54). The effects of two formulation factors (the ratio of citric acid/$NaHCO_3$ and the polyvidone content) and two process factors (the temperature and the velocity of the fluidizing air) on granule size, powder content, and dissolution rate of the tablets were studied using factorial design. In addition, the levels of the significant factors were optimized with the path of steepest ascent (46).

Solid dispersions of poorly water-soluble drugs were made by the fusion method. Citric acid was employed in various ratios with $NaHCO_3$ as the carrier for these drugs (55).

Stability

The greatest problem with effervescent products is the loss of reactivity with time if exposed prematurely to moisture (i.e., the stability of the effervescent system). In addition, the stability of the drug and some excipients, such as flavors, also must be considered.

Effervescent products are not stable in the presence of moisture. Most effervescent products are hygroscopic and can therefore adsorb enough moisture to initiate degradation if they are not suitably packaged.

Tablets made with equivalent amounts of $NaHCO_3$ and tartaric acid were stored at 70°C. In a closed system, a reaction between the $NaHCO_3$ and the tartaric acid occurred. When the tablets were stored as an open system, the weight loss was concluded to be a decarboxylation of the $NaHCO_3$ (56).

Effervescent compositions may be markedly stabilized if the $NaHCO_3$ is partly converted to the corresponding carbonate. Usually, the desired degree of stability is attained if approximately 2–10% of the weight of the bicarbonate is converted to the carbonate (57). The addition of sodium carbonate did not by itself improve stability. One explanation for the stabilizing effect caused by heating of the bicarbonate could be that heating causes a uniform distribution of the carbonate on the surface of the bicarbonate so that the water-scavenging efficiency is greater. Another explanation is that the carbonate formed by the rupture of the bicarbonate crystals would be much finer than added crystalline sodium carbonate, however finely ground. A third explanation is the possibility that double salts might be present and that they could be better scavengers than the carbonate itself (56). The moisture scavenging effect of potassium carbonate was determined and the concentration optimized for a specific formulation (27).

The stability of three commercial effervescent and one dispersible aspirin tablet were evaluated by factorially designed experiments. Temperature affected the hydrolysis of all tablets, whereas humidity influenced one product in a plastic tube and one in an aluminum tube (58).

Mercury-intrusion porosimetry and a cantilever beam-proximity transducer balance were used to monitor the stability of selected effervescent tablet systems. An index of reactivity was obtained from the balance measurements. The porosity measurements proved to be useful in elucidating tablet-pore structure changes over time.

Compression pressure and manufacturing conditions were not significant factors in the stability of an effervescent system when nonhygroscopic materials were used (54).

Codeine phosphate in a paracetamol-codeine effervescent tablet was found to react at room temperature with the citric acid constituents to form citrate esters of codeine. The esterification was confirmed in a solid-state reaction at an elevated temperature. Tartaric acid also yielded an ester with codeine phosphate in a similar nonsolvolytic reaction (59).

PRODUCTION

Granulation

At the Pharmacia plant in Helsingborg, Sweden, approximately 1200 kg of effervescent granulate is produced daily. Anhydrous citric acid and $NaHCO_3$ are massed with ethanol in a planetary mixer and the wet mass is dried on trays. Additional effervescent granulates are produced with vacuum equipment (Topo granulator) where water is the main component of the granulation liquid. The Topo granulator, developed for preparation of granules and coated particles in a vacuum, handles the mixing, granulation, drying, and milling/sieving as a closed system.

The fusion method, which employs heat to liberate water of crystallization from hydrous citric acid in order to effect moistening, was applied by using a high-shear mixer to generate heat (43). Batch sizes of 60 and 300 kg were granulated.

Anhydrous citric acid and $NaHCO_3$ were granulated with ethanol in a twin-screw extruder at powder flow rates of 60–90 kg/h in a continuous process (51).

The air suspension coating–reacting technique also is used in the production of effervescent granulates.

Tableting

Effervescent tablets are normally produced by machines with external lubrication systems. Most tablet machine manufacturers can add this type of equipment to their rotary machines. Products with a high proportion of acetylsalicylic acid can be manufactured without any traditional lubricants. Consequently, conventional rotary tablet presses can be used. Effervescent acetylsalicylic acid tablets are produced on ordinary high-speed rotary presses at the Pharmacia plant in Helsingborg, Sweden.

Effervescent granules can be tableted while still damp since moist citric acid acts as a lubricant. The compressed tablets are transferred immediately and continuously to ovens where they are dried. Drying also hardens them (44).

Several types of steel are normally used in the manufacture of compression tooling. Material rich in nickel was found to have the best resistance to rusting induced by a hydrochloride salt, although other factors, such as humidity, temperature, and contact time, also were responsible for the rusting of tooling material (60). This information may be useful when ordering and managing tooling materials for effervescent tablets.

The compression of effervescent mixtures usually results in severe picking and sticking. By means of flat-faced punches with discs of polytetrafluorethylene, the sticking to tablet-punch surfaces is overcome (61). Other nonadherent materials, such as Vulkollan® (a polyethane), Hostalit® (polyvinyl chloride), and Resopal® (a melamine), have been used (62). The disc of the plastic material is attached to the recess of the punch surface by glue or adhesive tape. It should be noted that fragments of the polymer can rub off during compression.

Effervescent tablets were produced using four different formulations that contained citric and/or tartaric acid and $NaHCO_3$ with polyvidone and PEG 6000. The adhesion of each formulation to the metal faces of the punch tips was determined by means of electron microscopy, surface-roughness measurements, and quantification of punch-weight variations during tablet production. The basic formulations were inherently adhesive and produced tablets with a weak, porous structure; the tablets were rougher than conventional, noneffervescent compressed tablets. Both formulations that contained tartaric acid produced tablets with a lower surface roughness and had less of a tendency to stick to tablet-punch faces than the two formulations that contained citric acid alone. The addition of a water-soluble sucrose ester had a beneficial effect, especially on formulations with inherently high adhesive tendencies (63).

In-Process Quality Control

For a rapid determination of loss on drying, an IR drying balance may be used. In the matter of size distribution, effervescent granulations are controlled by sieve analysis.

During the compression of effervescent tablets, in-process tests are routinely run to monitor the process. These tests include controls of tablet weight, weight variation, thickness, crushing strength, disintegration, and appearance of the tablet. Friability and pH of the solution may be additionally tested. Electronic devices that monitor tablet weight are normally used.

Inspection of the punches is carried out during the manufacturing of the tablets when plastic insertions are used. Inspections ensure that the plastic insertions are intact, i.e., that no loss or damage to the discs has occurred.

Product Evaluations

Both chemical and physical properties have to be considered when evaluating effervescent products. In this review, only the physical properties will be discussed, except where the chemical characteristics are especially influenced by the effervescent base. For more detail, Ph. Eur. includes a special disintegration test for effervescent tablets (1) and granules (8).

Many tests (e.g., titrimetric, gravimetric, colorimetric, and volumetric tests as well as loss-of-weight measurements and pressure measurements) have been proposed in order to determine carbon dioxide content (16, 48, 64). Methods based on monitoring carbon dioxide pressure generation and weight loss have been applied (16, 65).

Results from weight-loss measurements were modeled (65). Research indicates that the determination of water content by Karl Fischer analysis in effervescent tablets was possible after extraction with dioxane (66). $NaHCO_3$, which reacts with the Karl Fischer reagent, is insoluble in dioxane and does not interfere during the determination.

Near IR (NIR) is a quick and nondestructive method for the determination of water in effervescent products. In addition, it is suitable for in-process quality control. Measurement of pH of the solution is often performed. The conditions are important for congruent results.

Tablets

The disintegration and dissolution times are very important characteristics of effervescent products. A well-formulated effervescent tablet will disintegrate and dissolve within 1–2 min to form a clear solution. Consequently, the residue of undissolved drug must be minimal. The temperature of the water influences the dissolution time. It is, therefore, important to choose a water temperature that is actually used by consumers (e.g., cold tap water). Ph. Eur. includes a general requirement on disintegration time of 5 min in water 15–25°C (1).

Factors such as crushing strength and friability will influence the possibility of packaging the tablets on packaging lines, as effervescent tablets chip easily at the edges during handling. When the tablets are filled in tubes, the tablet height is of the utmost importance since the looseness or tightness of the packaging depends on the tablet height. When small or fairly small amounts of drug form part of the formulation, it is essential that content uniformity be carefully supervised.

Powders and Granules

Disintegration and dissolution time is an important characteristic, as is powder weight variation. The Ph. Eur. requirement time for disintegration of granules is 5 min (8).

Production Area

As the mass of an effervescent tablet is, as a rule, many times larger than that of a conventional tablet, larger amounts of raw material will have to be handled when packaging the same number of tablets. Therefore, the production area will be larger, too, unless a compact continuous line has been constructed.

At the Pharmacia plant in Helsingborg, Sweden, all steps during the production of effervescent tablets (i.e., mixing, granulating, drying, milling, final mixing of granulate and other constituents, tableting, and packaging) are performed in dehumidified areas of $<25\%$ RH and $<25°C$. Other companies perform mixing, granulating, drying, and milling at normal humidities but store the final mixture in dehumidified areas while slowly bubbling dehumidified air through the mixture. The mixture is then tableted and packaged in a small, dehumidified area around the tablet and packaging machine.

In direct compression, the mixing can be performed at normal humidities; however, in that case, the mixture is dried (to prevent a premature effervescent reaction) by means of causing dehumidified air to flow through the bed in a suitable container. Tableting and packaging are also performed in the dehumidified area. Thus, the number of manufacturing stages in the low humidity zone is reduced.

PACKAGING

Effervescent tablets should be stored in tightly closed containers or moisture-proof packs (6).

Even the moisture in the air may be enough to initiate the effervescent reaction of an effervescent product if it is not properly protected. When the consumer opens the

container, the effervescent product will again be exposed to the moisture in the air. Consequently, the packaging of all effervescent products is very important. The time between tablet production and start of packaging operation should be kept as short as possible.

Ph. Eur. recommends that effervescent granules and powders be stored in airtight containers (8). In the past, acidic and alkaline components were wrapped separately to prevent effervescent reactions during the storage of powders and granules.

Materials

Effervescent products are usually packed in individual aluminum foil pouches and effervescent tablets are often packed in metal tubes. To avoid excessive laminate stress, the dimensions of the sachets should be adapted to the dimensions of the tablet or the amount of granulate. These pouches are arranged in conveniently sized strips and stacked in a paperboard box.

The metal tube is a multiple-use container sealed with a moisture-proof closure. The tablets are stacked on top of one another. Consequently, a minimum of air surrounds them. The tubes are seamless, extruded aluminum packages. They are closed by tightly fitting plastic snap caps that contain a desiccant chamber. Tubes of plastic materials, such as polyvinyl chloride or polypropene, have been tested with effervescent tablets. Acceptable stability was obtained with some of these products. Plastic tubes are used more often due to their lower cost and lower noise level during the packaging operation.

Aluminum-foil blisters can provide hermetic packs. Similar protection can be achieved by using a foil-bearing laminate or a strip pack. A special strip pack for effervescent tablets, where each tablet is connected to a desiccant via a channel, has been suggested (67).

The effect of environmental moisture on the physical stability of effervescent tablets in foil-laminate packages containing microscopic imperfections was examined. Physical stability, after storing at different RH and temperature conditions, was assessed by noting whether the tablet components reacted prematurely. A penetrating dye-solution test was used in order to determine whether the foil packages permitted any transmission of moisture. High humidity accelerated the physical deterioration of effervescent tablets when stored in packets of poor integrity (68).

Filling

Packaging operations must be conducted in a low humidity environment if the long-term stability of the product is to be maintained. The tablets must be hard enough so as not to break during packaging.

Quality Control

Individual foil packets are tested for proper sealing. Several methods of rapid seal integrity testing have been devised, such as the vacuum underwater method, detection of tracer material sealed within the pouch, purging with detectable gas, IR seal inspection, and electronic air-tightness testers (3).

CONCLUSION

The traditional effervescent product is dissolved prior to oral intake. This requires the drug to have an acceptable taste. Since the drug is given as a solution, the absorption is normally rapid and the bioavailability is usually good.

The commercial manufacturing of effervescent products involves controlling air humidity in the production area. Special tablet machines are generally required, and the package is a very important part of the effervescent product. Over-the-counter analgesics have been very successful as effervescent tablets on certain markets.

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